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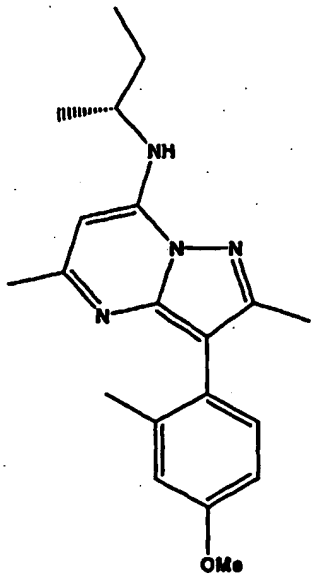
(54) Title: A CORTICOTROPIN RELEASING FACTOR RECEPTOR LIGAND, ITS ENANTIOMER AND PHARMACEUTICALLY ACCEPTABLE SALTS



(I)

(57) Abstract: Corticotropin releasing factor (CRF) antagonists of Formula (I) and its use in treating anxiety, depression, and other psychiatric, neurological disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress.

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A CORTICOTROPIN RELEASING FACTOR RECEPTOR LIGAND, ITS ENANTIOMER AND PHARMACEUTICALLY ACCEPTABLE SALTS

Field of the Invention

This invention relates to a treatment of psychiatric disorders and neurological diseases including major depression, anxiety-related disorders, post-traumatic stress disorder, supranuclear palsy and feeding disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psycho-pathological disturbances and stress, by administration of 7-(2-(*R*)-Butylamino)-2,5-dimethyl-3-(2-methyl-4-methoxyphenyl)-[1,5-a]pyrazolopyrimidine, its enantiomer or pharmaceutically acceptable salts thereof, as a corticotropin releasing factor receptor ligand.

Background of the Invention

Corticotropin releasing factor (herein referred to as CRF), a 41 amino acid peptide, is the primary physiological regulator of proopiomelanocortin (POMC) - derived peptide secretion from the anterior pituitary gland [J. Rivier et al., *Proc. Nat. Acad. Sci. (USA)* 80:4851 (1983); W. Vale et al., *Science* 213:1394 (1981)]. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad

extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in brain [W. Vale et al., *Rec. Prog. Horm. Res.* 39:245 (**1983**); G.F. Koob, *Persp. Behav. Med.* 2:39 (**1985**); E.B. De Souza et al., *J. Neurosci.* 5:3189 (**1985**)]. There is also evidence that CRF plays a significant role in integrating the response of the immune system to physiological, psychological, and immunological stressors [J.E. Blalock, *Physiological Reviews* 69:1 (**1989**); J.E. Morley, *Life Sci.* 41:527 (**1987**)].

Clinical data provide evidence that CRF has a role in psychiatric disorders and neurological diseases including depression, anxiety-related disorders and feeding disorders. A role for CRF has also been postulated in the etiology and pathophysiology of Alzheimer's disease, Parkinson's disease, Huntington's disease, progressive supranuclear palsy and amyotrophic lateral sclerosis as they relate to the dysfunction of CRF neurons in the central nervous system [for review see E.B. De Souza, *Hosp. Practice* 23:59 (**1988**)].

In affective disorder, or major depression, the concentration of CRF is significantly increased in the cerebrospinal fluid (CSF) of drug-free individuals [C.B.

Nemeroff et al., *Science* 226:1342 (1984); C.M. Banki et al., *Am. J. Psychiatry* 144:873 (1987); R.D. France et al., *Biol. Psychiatry* 28:86 (1988); M. Arato et al., *Biol Psychiatry* 25:355 (1989)]. Furthermore, the density of CRF receptors is significantly decreased in the frontal cortex of suicide victims, consistent with a hypersecretion of CRF [C.B. Nemeroff et al., *Arch. Gen. Psychiatry* 45:577 (1988)]. In addition, there is a blunted adrenocorticotropin (ACTH) response to CRF (i.v. administered) observed in depressed patients [P.W. Gold et al., *Am J. Psychiatry* 141:619 (1984); F. Holsboer et al., *Psychoneuroendocrinology* 9:147 (1984); P.W. Gold et al., *New Eng. J. Med.* 314:1129 (1986)]. Preclinical studies in rats and non-human primates provide additional support for the hypothesis that hypersecretion of CRF may be involved in the symptoms seen in human depression [R.M. Sapolsky, *Arch. Gen. Psychiatry* 46:1047 (1989)]. There is preliminary evidence that tricyclic antidepressants can alter CRF levels and thus modulate the numbers of CRF receptors in brain [Grigoriadis et al., *Neuropsychopharmacology* 2:53 (1989)].

It has also been postulated that CRF has a role in the etiology of anxiety-related disorders. CRF produces

anxiogenic effects in animals and interactions between benzodiazepine / non-benzodiazepine anxiolytics and CRF have been demonstrated in a variety of behavioral anxiety models [D.R. Britton et al., *Life Sci.* 31:363 (1982); C.W. Berridge and A.J. Dunn *Regul. Peptides* 16:83 (1986)]. Preliminary studies using the putative CRF receptor antagonist a-helical ovine CRF (9-41) in a variety of behavioral paradigms demonstrate that the antagonist produces "anxiolytic-like" effects that are qualitatively similar to the benzodiazepines [C.W. Berridge and A.J. Dunn *Horm. Behav.* 21:393 (1987), *Brain Research Reviews* 15:71 (1990)].

Neurochemical, endocrine and receptor binding studies have all demonstrated interactions between CRF and benzodiazepine anxiolytics, providing further evidence for the involvement of CRF in these disorders. Chlordiazepoxide attenuates the "anxiogenic" effects of CRF in both the conflict test [K.T. Britton et al., *Psychopharmacology* 86:170 (1985); K.T. Britton et al., *Psychopharmacology* 94:306 (1988)] and in the acoustic startle test [N.R. Swerdlow et al., *Psychopharmacology* 88:147 (1986)] in rats. The benzodiazepine receptor antagonist (Ro15-1788), which was without behavioral activity alone in the operant conflict test, reversed

the effects of CRF in a dose-dependent manner while the benzodiazepine inverse agonist (FG7142) enhanced the actions of CRF [K.T. Britton et al., *Psychopharmacology* 94:306 (1988)].

The mechanisms and sites of action through which the standard anxiolytics and antidepressants produce their therapeutic effects remain to be elucidated. It has been hypothesized however, that they are involved in the suppression of the CRF hypersecretion that is observed in these disorders. Of particular interest is that preliminary studies examining the effects of a CRF receptor antagonist (a-helical CRF9-41) in a variety of behavioral paradigms have demonstrated that the CRF antagonist produces "anxiolytic-like" effects qualitatively similar to the benzodiazepines [for review see G.F. Koob and K.T. Britton, In: *Corticotropin-Releasing Factor: Basic and Clinical Studies of a Neuropeptide*, E.B. De Souza and C.B. Nemeroff eds., CRC Press p221 (1990)].

It has been further postulated that CRF has a role in cardiovascular or heart-related diseases as well as gastrointestinal disorders arising from stress such as hypertension, tachycardia and congestive heart failure, stroke, irritable bowel syndrome post-operative ileus and colonic hypersensitivity associated with

psychopathological disturbance and stress [for reviews see E.D. DeSouza, C.B. Nemeroff, Editors; *Corticotropin-Releasing Factor: Basic and Clinical Studies of a Neuropeptide*, E.B. De Souza and C.B. Nemeroff eds., CRC Press p221 (1990) and C. Maillot, M. Million, J.Y. Wei, A. Gauthier, Y. Tache, Gastroenterology, 119, 1569-1579 (2000)].

Over-expression or under -expression of CRF has been proposed as an underlying cause for several medical disorders. Such treatable disorders include, for example and without limitation: affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia, hypertension, tachycardia and congestive heart failure, stroke, osteoporosis, premature birth, psychosocial dwarfism, stress-induced fever, ulcer, diarrhea, post-

operative ileus and colonic hypersensitivity associated with psychopathological disturbance and stress [for reviews see J.R. McCarthy, S.C. Heinrichs and D.E. Grigoriadis, Cuur. Pharm. Res., 5, 289-315 (1999); P.J. Gilligan, D.W. Robertson and R. Zaczek, J. Medicinal Chem., 43, 1641-1660 (2000), G. P. Chrousos, Int. J. Obesity, 24, Suppl. 2, S50-S55 (2000); E. Webster, D.J. Torpy, I.J. Elenkov, G.P. Chrousos, Ann. N.Y. Acad. Sci., 840, 21-32 (1998); D.J. Newport and C.B. Nemeroff, Curr. Opin. Neurobiology, 10, 211-218 (2000); G. Mastorakos and I. Ilias, Ann. N.Y. Acad. Sci., 900, 95-106 (2000); M.J. Owens and C.B. Nemeroff, Expert Opin. Invest. Drugs, 8, 1849-1858 (1999); G. F. Koob, Ann. N.Y. Acad. Sci., 909, 170-185 (2000)].

The following publications each describe CRF antagonist compounds; however, none disclose the compounds provided herein: WO95/10506; WO99/51608; WO97/35539; WO99/01439; WO97/44308; WO97/35846; WO98/03510; WO99/11643; PCT/US99/18707; WO99/01454; and, WO00/01675.

Summary of the Invention

In accordance with one aspect, the present invention provides a novel compound, pharmaceutical compositions and methods which may be used in the treatment of affective disorder, anxiety, depression,

irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal disease, anorexia nervosa or other feeding disorder, drug or alcohol withdrawal symptoms, drug addiction, inflammatory disorder, fertility problems, disorders, the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, or a disorder selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic, phobias, obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress-induced headache; cancer, human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's

disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases such as ulcers, irritable bowel syndrome, Crohn's disease, spastic colon, diarrhea, and post operative ilius and colonic hypersensitivity associated by psychopathological disturbances or stress; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone (ADH); obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage (e.g., cerebral ischemia such as cerebral hippocampal ischemia); excitotoxic neuronal damage; epilepsy; cardiovascular and hear related disorders including hypertension, tachycardia and congestive heart failure; stroke; immune dysfunctions including stress induced immune dysfunctions (e.g., stress induced fevers, porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, and dysfunctions induced by confinement in chickens, sheering stress in sheep or human-animal interaction related stress in dogs); muscular spasms; urinary incontinence; senile dementia of the Alzheimer's

type; multiinfarct dementia; amyotrophic lateral sclerosis; chemical dependencies and addictions (e.g., dependencies on alcohol, cocaine, heroin, benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; osteoporosis; psychosocial dwarfism and hypoglycemia in a mammal.

The present invention provides a novel compound which binds to corticotropin releasing factor receptors, thereby altering the anxiogenic effects of CRF secretion. The compound of the present invention is useful for the treatment of psychiatric disorders and neurological diseases, anxiety-related disorders, post-traumatic stress disorder, supranuclear palsy and feeding disorders as well as treatment of immunological, cardiovascular or heart-related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress in a mammal.

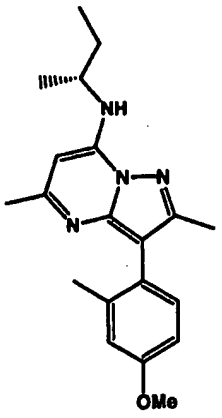
According to another aspect, the present invention provides a novel compound of Formula (I) (described below) which is useful as an antagonist of the corticotropin releasing factor. The compound of the present invention exhibits activity as a

corticotropin releasing factor antagonist and appears to suppress CRF hypersecretion. The present invention also includes pharmaceutical compositions containing such a compound of Formula (I), and methods of using such a compound for the suppression of CRF hypersecretion, and/or for the treatment of anxiogenic disorders.

According to yet another aspect of the invention, the compound provided by this invention (and especially the labelled compound of this invention) is also useful as a standard and reagent in determining the ability of a potential pharmaceutical to bind to the CRF receptor.

Detailed Description of the Invention

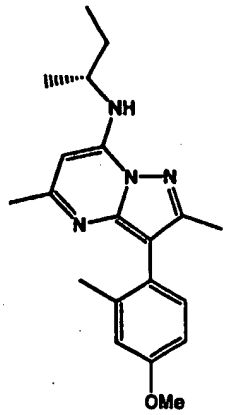
The present invention comprises a compound of Formula (I):



(I)

and stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

The present invention also comprises a method of treating affective disorder, anxiety, depression, headache, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa or other feeding disorder, drug addiction, drug or alcohol withdrawal symptoms, inflammatory diseases, cardiovascular or heart-related diseases, fertility problems, human immunodeficiency virus infections, hemorrhagic stress, obesity, infertility, head and spinal cord traumas, epilepsy, stroke, ulcers, amyotrophic lateral sclerosis, hypoglycemia or a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, in mammals comprising administering to the mammal a therapeutically effective amount of a compound of Formula (I):



(I)

and stereoisomeric forms thereof, or mixtures of stereoisomeric forms thereof, and pharmaceutically acceptable salt or pro-drug forms thereof.

As used herein, the term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic acids, including inorganic acids and organic acids. Suitable non-toxic acids include inorganic and organic acids of basic residues such as amines, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric acid, p-toluenesulfonic and the like; and alkali or organic salts of acidic residues such as carboxylic acids, for example, alkali and alkaline earth metal salts derived from the following bases: sodium hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminum hydroxide, lithium hydroxide, magnesium hydroxide, zinc hydroxide, ammonia, trimethylammonia, triethylammonia, ethylenediamine, n-methyl-glucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine,chloroprocaine, diethanolamine, procaine, n-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide,and the like. Pharmaceutically acceptable salts of the compounds of the invention can be prepared by

reacting the free acid or base forms of the compound with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

"Pharmaceutically acceptable prodrugs" as used herein means any covalently bonded carriers which release the active parent drug of Formula (I) in vivo when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of Formula (I) are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "prodrug" means compounds that are rapidly transformed in vivo to yield the parent compound of formula (I), for example by hydrolysis in blood. Functional groups which may be rapidly transformed, by metabolic cleavage, in vivo form a class of groups reactive with the carboxyl group of the compounds of this invention. They include, but are not limited to such groups as

alkanoyl (such as acetyl, propionyl, butyryl, and the like), unsubstituted and substituted aroyl (such as benzoyl and substituted benzoyl), alkoxycarbonyl (such as ethoxycarbonyl), trialkylsilyl (such as trimethyl- and triethysilyl), monoesters formed with dicarboxylic acids (such as succinyl), and the like. Because of the ease with which the metabolically cleavable groups of the compounds useful according to this invention are cleaved in vivo, the compounds bearing such groups act as pro-drugs. The compounds bearing the metabolically cleavable groups have the advantage that they may exhibit improved bioavailability as a result of enhanced solubility and/or rate of absorption conferred upon the parent compound by virtue of the presence of the metabolically cleavable group. A thorough discussion of prodrugs is provided in the following: Design of Prodrugs, H. Bundgaard, ed., Elsevier, 1985; Methods in Enzymology, K. Widder et al, Ed., Academic Press, 42, p.309-396, 1985; A Textbook of Drug Design and Development, Krogsgaard-Larsen and H. Bundgaard, ed., Chapter 5; "Design and Applications of Prodrugs" p.113-191, 1991; Advanced Drug Delivery Reviews, H. Bundgard, 8, p.1-38, 1992; Journal of Pharmaceutical Sciences, 77, p. 285, 1988; Chem. Pharm. Bull., N. Nakeya et al, 32, p. 692, 1984; Pro-drugs as Novel Delivery Systems, T. Higuchi and V. Stella, Vol. 14 of the A.C.S. Symposium Series, and Bioreversible Carriers in Drug Design, Edward B. Roche, ed., American Pharmaceutical Association and Pergamon

Press, 1987, which are incorporated herein by reference.

"Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug of Formula (I) in vivo when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of Formula (I) are prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compounds. Prodrugs include compounds wherein hydroxy, amine, or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of Formula (I), and the like.

As used herein to describe a compound, the term "substantially free of its (+) stereoisomer" means that the compound is made up of a significantly greater proportion of its (-) stereoisomer than of its optical antipode (i.e., its (+) stereoisomer). In a preferred embodiment of the invention, the term "substantially free of its (+) stereoisomer" means that the compound is made up of at least about 90% by weight of its (-) stereoisomer and about 10% by weight or less of its (+) stereoisomer.

In a more preferred embodiment of the invention, the term "substantially free of its (+) stereoisomer"

means that the compound is made up of at least about 95% by weight of its (-) stereoisomer and about 5% by weight or less of its (+) stereoisomer. In an even more preferred embodiment, the term "substantially free of its (+) stereoisomer" means that the compound is made up of at least about 99% by weight of its (-) stereoisomer and about 1% or less of its (+) stereoisomer. In another preferred embodiment, the term "substantially free of its (+) stereoisomer" means that the compound is made up of nearly 100% by weight of its (-) stereoisomer. The above percentages are based on the total amount of the combined stereoisomers of the compound.

The term "therapeutically effective amount" of a compound of this invention means an amount effective to antagonize abnormal level of CRF or treat the symptoms of affective disorder, anxiety or depression in a host.

Synthesis

Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these compounds, called

stereoisomers, are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture.

The present invention includes all stereoisomeric forms of the compounds of the formula I. Centers of asymmetry that are present in the compounds of formula I can all independently of one another have S configuration or R configuration. The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. The invention includes all possible enantiomers and diastereomers and mixtures of two or more stereoisomers, for example mixtures of enantiomers and/or diastereomers, in all ratios. Thus, enantiomers are a subject of the invention in enantiomerically pure form, both as levorotatory and as dextrorotatory antipodes, in the form of racemates and in the form of mixtures of the two enantiomers in all ratios. In the case of a cis/trans isomerism the invention includes both the cis form and the trans form as well as mixtures of these forms in all ratios. The preparation of individual stereoisomers can be carried out, if desired, by separation of a mixture by customary methods, for example by chromatography or crystallization, by the use of stereochemically uniform starting materials for the

synthesis or by stereoselective synthesis. Optionally a derivatization can be carried out before a separation of stereoisomers. The separation of a mixture of stereoisomers can be carried out at the stage of the compounds of the formula I or at the stage of an intermediate during the synthesis. The present invention also includes all tautomeric forms of the compounds of formula (I).

A compound of Formula (I) may be prepared from using the procedures outlined in Scheme 1.

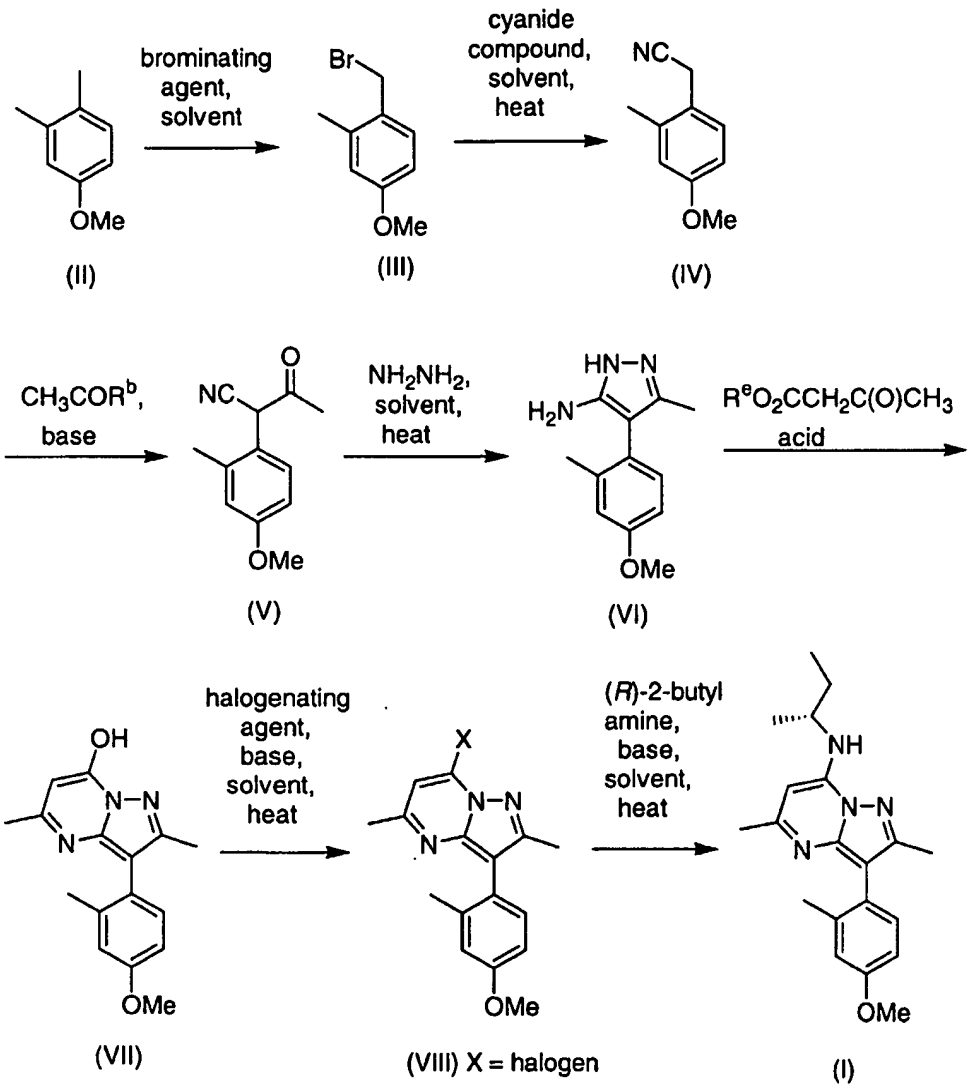
A compound of Formula (II) is reacted with brominating agents (e.g. N-bromosuccinimide / 2,2'-azobisisobutyronitrile (AIBN) or N-bromophthalimide / 2,2'-azobisisobutyronitrile (AIBN)) in the presence of an inert solvent (e.g. halocarbons (1 to 6 carbons, 1 to 6 halogens (preferably chlorine)) at reaction temperatures ranging from 50°C to 200°C (preferably 50°C to 120°C) to afford a compound of Formula (III).

A compound of Formula (III) is reacted with cyanide compounds (e.g. sodium cyanide, potassium cyanide) in the presence of an inert solvent (e.g. N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide))at

reaction temperatures ranging from 50°C to 250°C (preferably 50°C to 180°C) to afford a compound of Formula (IV).

A compound of the Formula (IV) is reacted with compounds of the formula CH_3COR^b, where R^b is halogen, cyano, lower alkoxy (1 to 6 carbons) or lower alkanoyloxy (1 to 6 carbons), in the presence of a base in an inert solvent at reaction temperatures ranging from -78°C to 200°C to afford a compound of Formula (V).

Scheme 1



Bases may include, but are not limited to, alkali metals, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons) (preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal

dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal hydroxides, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine) or aromatic amines (preferably pyridine).

Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), water, dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C.

Compounds of Formula (V) may be treated with hydrazine-hydrate in the presence of an inert solvent at temperatures ranging from 0°C to 200°C, preferably 70°C to 150°C, to produce compounds of Formula (VI). Inert solvents may include, but are not limited to, water, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons,

preferably acetonitrile), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene).

A compound of Formula (VI) may be treated with compounds of $CH_3COCH_2CO_2R^e$, where R^e is alkyl (1 - 6 carbons), in the presence or absence of acid in an inert solvent at temperatures ranging from 0°C to 250°C to give a compound of Formula (VII). Acids may include, but are not limited to alkanoic acids of 2 to 10 carbons (preferably acetic acid), haloalkanoic acids (2 - 10 carbons, 1-10 halogens, such as trifluoroacetic acid), arylsulfonic acids (preferably p-toluenesulfonic acid or benzenesulfonic acid), alkanesulfonic acids of 1 to 10 carbons (preferably methanesulfonic acid), hydrochloric acid, sulfuric acid or phosphoric acid. Stoichiometric or catalytic amounts of such acids may be used.

Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably

tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide) or aromatic hydrocarbons (preferably benzene or toluene). Preferred reaction temperatures range from 0°C to 100°C.

A compound of Formula (VII) may be treated with a halogenating agent in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from 50°C to 250°C to give a product of Formula (VIII) (where X is halogen). Halogenating agents include, but are not limited to, $SOCl_2$, $POCl_3$, PCl_3, PCl_5, $POBr_3$, PBr_3 or PBr_5. Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably N,N-di-isopropyl-N-ethyl amine or triethylamine) or aromatic amines (preferably pyridine).

Inert solvents may include, but are not limited to, lower alkanenitriles (1 to 6 carbons, preferably

acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloroethane). Preferred reaction temperatures range from 80°C to 180°C.

A compound of Formula (VIII) may be reacted with a compound of Formula $CH_3(CH_3CH_2)CHNH_2$ in the presence or absence of a base in the presence or absence of an inert solvent at reaction temperatures ranging from -80°C to 250°C to generate a compound of Formula (I). Bases may include, but are not limited to, alkali metal hydrides (preferably sodium hydride), alkali metal alkoxides (1 to 6 carbons)(preferably sodium methoxide or sodium ethoxide), alkaline earth metal hydrides, alkali metal dialkylamides (preferably lithium di-isopropylamide), alkali metal carbonates, alkali metal bicarbonates, alkali metal bis(trialkylsilyl)amides (preferably sodium bis(trimethylsilyl)amide), trialkyl amines (preferably

N,N-di-isopropyl-N-ethyl amine) or aromatic amines (preferably pyridine).

Inert solvents may include, but are not limited to, alkyl alcohols (1 to 8 carbons, preferably methanol or ethanol), lower alkanenitriles (1 to 6 carbons, preferably acetonitrile), dialkyl ethers (preferably diethyl ether), cyclic ethers (preferably tetrahydrofuran or 1,4-dioxane), N,N-dialkylformamides (preferably dimethylformamide), N,N-dialkylacetamides (preferably dimethylacetamide), cyclic amides (preferably N-methylpyrrolidin-2-one), dialkylsulfoxides (preferably dimethylsulfoxide), aromatic hydrocarbons (preferably benzene or toluene) or haloalkanes of 1 to 10 carbons and 1 to 10 halogens (preferably dichloromethane). Preferred reaction temperatures range from 0°C to 140°C.

EXAMPLES

Analytical data were recorded for the compounds described below using the following general procedures. Proton NMR spectra were recorded on a Varian VXR or Unity 300 FT-NMR instruments(300 MHz); chemical shifts were recorded in ppm (δ) from an internal tetramethysilane standard in deuterochloroform or deuterodimethylsulfoxide as specified below. Mass spectra (MS) or high resolution mass spectra (HRMS) were

recorded on a Finnegan MAT 8230 spectrometer or a Hewlett Packard 5988A model spectrometer (using chemi-ionization (CI) with NH_3 as the carrier gas, electrospray (ESI) or gas chromatography (GC)). Melting points were recorded on a MelTemp 3.0 heating block apparatus and are uncorrected. Boiling points are uncorrected. All pH determinations during workup were made with indicator paper.

Reagents were purchased from commercial sources and, where necessary, purified prior to use according to the general procedures outlined by D. Perrin and W.L.F. Armarego, *Purification of Laboratory Chemicals*, 3rd ed., (New York: Pergamon Press, 1988). Chromatography was performed on silica gel using the solvent systems indicated below. For mixed solvent systems, the volume ratios are given. Otherwise, parts and percentages are by weight. Commonly used abbreviations are: DMF (N,N-dimethylformamide), EtOH (ethanol), MeOH (methanol), EtOAc (ethyl acetate), HOAc (acetic acid) and THF (tetrahydrofuran).

The following examples are provided to describe the invention in further detail. These examples, which set forth the best mode presently contemplated for carrying out the invention, are intended to illustrate and not to limit the invention.

EXAMPLE 1

Preparation of 7-hydroxy-5-methyl-3-(2-methyl-4-methoxyphenyl)pyrazolo[1,5-a]pyrimidine

A. 2-Methyl-4-methoxyphenylacetonitrile

A mixture of 3,4-dimethylanisole (24.5 g, 180 mmol), N-bromosuccinimide (32.0 g, 180 mmol) and AIBN (1.0 g) in carbon tetrachloride (350 mL) was stirred at reflux temperature for 2 h. The reaction mixture was cooled to ambient temperature and filtered. Solvent was removed from the filtrate in vacuo to give crude 2-methyl-4-methoxyphenylbenzyl bromide as a yellow oil.

The above oil was aded portionwise to a refluxing mixture of sodium cyanide (12.3 g, 250 mmol) in a mixture of DMF(75 mL), EtOH (500 mL) and water (250 mL) with stirring. After being cooled to ambient temperature, the reaction mixture was diluted with water (1 L) and extracted three times with EtOAc (25 mL). The combined organic layers were washed with brine, dried over MgSO4 and filtered. Solvent was removed in vacuo to provide an oily solid. Column chromatography (EtOAC:hexanes::1:9) afforded 2-methyl-4-methoxyphenylacetonitrile (6.5 g): NMR ($CDCl_3$,300 MHz): 7.25 (br d, 1H, J = 8, 1), 6.80 - 6.70 (m, 2H), 3.80 (s, 3H), 3.60 (s, 2H), GC-MS: 162 (M + H).

B. 1-Cyano-1-(2-methyl4-methoxyphenyl)propan-2-one

Sodium pellets 1.2 g, 52.2 mmol) were added portionwise to a solution of 2-methyl-4-methoxyphenylacetonitrile (6.5 g, 40.4 mol) in ethyl acetate (150 mL) at ambient temperature. The reaction mixture was heated to reflux temperature and stirred for 16 hours. The resulting suspension was cooled to room temperature and filtered. The collected precipitate was washed with copious amounts of ether and then air-dried. The solid was dissolved in water and a 1N HCl solution was added until the pH = 5-6. The mixture was extracted with ethyl acetate (3 X 200 mL); the combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo* to afford a white solid (4.5g): NMR ($CDCl_3$,300 MHz): 7.30 (dd, 1H, J = 8, 1), 6.85 - 6.75 (m, 2H), 4.75 (s, 1H), 3.8 (s, 3H), 2.3 (s, 3H), 2.2 (s, 3H); CI-MS: 204 (M + H).

C. 5-Amino-4-(2-methyl-4-methoxyphenyl)-3-methylpyrazole

A mixture of 1-cyano-1-(2-methyl-4-methoxyphenyl)propan-2-one (4.5 g, 22.2 mol), hydrazine-hydrate (2.1 mL, 44.4 mol), glacial acetic acid (4.3 mL, 75 mol) and toluene (57 mL) were stirred at reflux temperature for 18 hours in an apparatus fitted with a Dean-Stark trap. The reaction mixture was cooled to ambient temperature and solvent was removed in vacuo.

The residue was dissolved in 6N HCl and the resulting solution was extracted with ether three times. A concentrated sodium hydroxide solution was added to the aqueous layer until pH = 11. The resulting semi-solution was extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and filtered. Solvent was removed *in vacuo* to give a viscous oil (4.0 g): NMR ($CDCl_3$, 300 MHz): 7.10 (d, 1H, J = 8), 6.85 (d, 1H, J=1), 6.80 (dd, 1H, J = 8, 1), 3.85 (s, 3H), 2.2 (s, 3H), 2.15-2.0 (m, 2H), b2.10 (s, 3H); MS: 218 (M + H).

D. 7-hydroxy-2,5-dimethyl-3-(2-methyl-4-methoxyphenyl)-pyrazolo[1,5-a]pyrimidine

5-Amino-4-(2-methyl-4-methoxyphenyl)-3-methylpyrazole (14.5 g, 66.7 mmol) was dissolved in glacial acetic acid (45 mL) with stirring. Ethyl acetoacetate (10.2 mL, 80.1 mmol) was then added dropwise to the resulting solution. The reaction mixture was then heated to reflux temperature and stirred for 16 hours, then cooled to room temperature. Ether (100 mL) was added and the resulting precipitate was collected by filtration. Drying in vacuo afforded a white solid (14.7 g): NMR ($CDCl_3$, 300Hz): 11.7 (br.s 1H), 7.12 (d, 1H, J = 8), 6.94 (d, 1H, J = 3), 6.84 (dd,

1H, J = 8,3), 5.53 (s, 1H), 3.79 (s, 3H), 3.34 (s, 1H), 2.23 (s, 6H), 2.07 (s, 3H); MS: 283 (M+H).

EXAMPLE 2

7-chloro-2,5-dimethyl -3-(2-methyl-4-methoxyphenyl)-pyrazolo[1,5-a]pyrimidine

A mixture of 7-hydroxy-2,5-dimethyl 5-methyl-3-(2-methyl-4-methoxyphenyl)-pyrazolo[1,5-a]pyrimidine (2.83 g, 10.0 mmol), phosphorus oxychloride (6.1 g, 3.7 mL, 40 mmol), di-isopropylethylamine (5.2 g, 7.0 mL, 40 mmol) and toluene (80 mL) was stirred at reflux temperature for 3 hours, then it was cooled to ambient temperature. The volatiles were removed in vacuo. Flash chromatography (EtOAc:hexane::1:4) on the residue gave the title compound (1.2g) as an oil: NMR ($CDCl_3$, 300Hz): 7.16 (d, 1H, J = 8), 6.89 (d, 1H, J = 2), 6.82 (dd, 1H, J = 8, 2), 6.78 (s, 1H), 3.84 (3, 3H), 2.53 (s, 3H), 2.42 (s, 3H), 2.16 (s, 3H); MS: 302, 304 (M+H).

EXAMPLE 3

7-(2-(R)-Butylamino)-2,5-dimethyl-3-(2-methyl-4-methoxyphenyl)-[1,5-a]pyrazolopyrimidine

A solution of (R)-2-butylamine (6.8 g, 5.0 mL, 93 mmol) and 7-chloro-2,5-dimethyl-3-(2-methyl-4-methoxyphenyl)pyrazolo[1,5-a]pyrimidine (1.2 g, 4 mmol)

was stirred at reflux temperature for 2 hours; then it was cooled to ambient temperature. The reaction mixture was then poured onto water (100 mL) and mixed. Three extractions with dichloromethane, washing the combined organic layers with brine, drying over $MgSO_4$, and filtration through silica gel on celite afforded a white solid (1.0): mp = 123.0 °C ; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.17 (d, 1H, J = 8), 6.86 (d, 1H, J = 3), 6.78 (dd, 1H, J = 8, 3), 6.03 (d, 1H, J = 8), 5.77 (s, 1H), 3.82 (s, 3H), 3.65 - 3.60 (m, 1H), 2.45 (s, 3H), 2.33 (s, 3H), 2.20 (s, 3H), 1.76-1.66 (m, 2H), 1.35 (d, 3H, J = 7), 1.03 (t, 3H, J = 7); ^{13}C-NMR ($CDCl_3$, 100.52 MHz): δ 159.0, 158.9, 151.8, 146.6, 145.3, 139.7, 132.6, 124.5, 115.7, 111.1, 107.5, 85.0, 55.2, 49.5, 29.7, 25.4, 20.7, 20.3, 13.2, 10.5; IR (neat, KBr, cm^{-1}): 3245 (br, s), 3000 (m), 2969 (s), 2927 (s), 1617 (s), 1583 (s), 1556 (s), 1502 (s), 1473 (s), 1462 (s), 1453 (s), 1427 (s), 1379 (m), 1364 (m), 1323 (s), 1290 (s), 1254 (m), 1237 (s), 1226 (m), 1185 (m), 1158 (s), 1121 (s), 1110 (m), 1053 (m), 1037 (m), 1002 (s); $[\alpha]_D^{25}$ = -37.6° (c = 0.628 g/dL, CH_3OH); ESI(+)-HRMS: Calcd for $C_{20}H_{26}N_4O$: 339.2185; Found: 339.2185 (M^+ + H). Anal. Calcd for $C_{20}H_{26}N_4O$: C, 70.98, H, 7.74, N, 16.55; Found: C, 71.06, H, 7.70, N, 16.50.

Utility

Rat CRF Receptor Binding Assay for the Evaluation of Biological Activity

Receptor binding affinity to rat cortical receptors was assayed according to the published methods (E.B. De Souza, *J. Neuroscience*, 7: 88 (**1987**).

Curves of the inhibition of [^{125}I-Tyr^{0}]-o-CRF binding to cell membranes at various dilutions of test drug were analyzed by the iterative curve fitting program LIGAND [P.J. Munson and D. Rodbard, *Anal. Biochem.* 107:220 (**1980**), which provides Ki values for inhibition which are then used to assess biological activity.

Inhibition of CRF-Stimulated Adenylate Cyclase Activity

Inhibition of CRF-stimulated adenylate cyclase activity can be performed as described by G. Battaglia et al. *Synapse* **1**:572 (**1987**). Briefly, assays are carried out at 37° C for 10 min in 200 ml of buffer containing 100 mM Tris-HCl (pH 7.4 at 37° C), 10 mM $MgCl_2$, 0.4 mM EGTA, 0.1% BSA, 1 mM isobutylmethylxanthine (IBMX), 250 units/ml phosphocreatine kinase, 5 mM creatine phosphate, 100 mM guanosine 5'-triphosphate, 100 nM oCRF, antagonist

peptides (concentration range 10^{-9} to 10^{-6}m) and 0.8 mg original wet weight tissue (approximately 40-60 mg protein). Reactions are initiated by the addition of 1 mM ATP/^{32}P]ATP (approximately 2-4 mCi/tube) and terminated by the addition of 100 ml of 50 mM Tris-HCL, 45 mM ATP and 2% sodium dodecyl sulfate. In order to monitor the recovery of cAMP, 1 µl of [^{3}H]cAMP (approximately 40,000 dpm) is added to each tube prior to separation. The separation of [^{32}P]cAMP from [^{32}P]ATP is performed by sequential elution over Dowex and alumina columns.

In vivo Biological Assay

The *in vivo* activity of a compound of the present invention can be assessed using any one of the biological assays available and accepted within the art. Illustrative of these tests include the Acoustic Startle Assay, the Stair Climbing Test, and the Chronic Administration Assay. These and other models useful for the testing of compounds of the present invention have been outlined in C.W. Berridge and A.J. Dunn *Brain Research Reviews* 15:71 (**1990**).

A compound may be tested in any species of rodent or small mammal.

A compound of this invention has utility in the treatment of imbalances associated with abnormal levels of corticotropin releasing factor in patients suffering from depression, affective disorders, and/or anxiety.

A compound of this invention can be administered to treat these abnormalities by means that produce contact of the active agent with the agent's site of action in the body of a mammal. The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals either as individual therapeutic agent or in combination of therapeutic agents. It can be administered alone, but will generally be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will vary depending on the use and known factors such as pharmacodynamic character of the particular agent, and its mode and route of administration; the recipient's age, weight, and health; nature and extent of symptoms; kind of concurrent treatment; frequency of treatment; and desired effect. For use in the treatment of said diseases or conditions, a compound of this invention can be orally administered daily at a dosage of the

active ingredient of 0.002 to 200 mg/kg of body weight. Ordinarily, a dose of 0.01 to 10 mg/kg in divided doses one to four times a day, or in sustained release formulation will be effective in obtaining the desired pharmacological effect.

Dosage forms (compositions) suitable for administration contain from about 1 mg to about 100 mg of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be present in an amount of about 0.5 to 95% by weight based on the total weight of the composition.

The active ingredient can be administered orally is solid dosage forms, such as capsules, tablets and powders; or in liquid forms such as elixirs, syrups, and/or suspensions. The compounds of this invention can also be administered parenterally in sterile liquid dose formulations.

Gelatin capsules can be used to contain the active ingredient and a suitable carrier such as but not limited to lactose, starch, magnesium stearate, steric acid, or cellulose derivatives. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of

medication over a period of time. Compressed tablets can be sugar-coated or film-coated to mask any unpleasant taste, or used to protect the active ingredients from the atmosphere, or to allow selective disintegration of the tablet in the gastrointestinal tract.

Liquid dose forms for oral administration can contain coloring or flavoring agents to increase patient acceptance.

In general, water, pharmaceutically acceptable oils, saline, aqueous dextrose (glucose), and related sugar solutions and glycols, such as propylene glycol or polyethylene glycol, are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, butter substances. Antioxidizing agents, such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or in combination, are suitable stabilizing agents. Also used are citric acid and its salts, and EDTA. In addition, parenteral solutions can contain preservatives such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences", A. Osol, a standard reference in the field.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of units capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 mg of powdered active ingredient, 150 mg lactose, 50 mg cellulose, and 6 mg magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean, cottonseed oil, or olive oil is prepared and injected by means of a positive displacement was pumped into gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules were washed and dried.

Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit was 100 mg active ingredient, 0.2 mg of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch, and 98.8

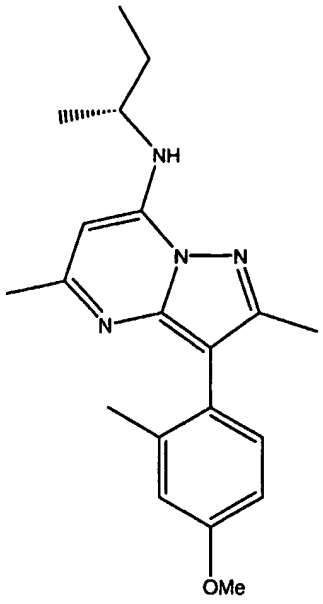
mg lactose. Appropriate coatings may be applied to increase palatability or delayed adsorption.

The compounds of this invention may also be used as reagents or standards in the biochemical study of neurological function, dysfunction, and disease.

Although the present invention has been described and exemplified in terms of certain preferred embodiments, other embodiments will be apparent to those skilled in the art. The invention is, therefore, not limited to the particular embodiments described and exemplified, but is capable of modification or variation without departing from the spirit of the invention, the full scope of which is delineated by the appended claims.

What is claimed is

1. A compound of Formula (I):



(I)

or isomers thereof, stereoisomeric forms thereof, mixtures of stereoisomeric forms thereof, pharmaceutically acceptable prodrugs thereof, or pharmaceutically acceptable salt forms.

2. A compound of claim 1, isomers thereof, stereoisomeric forms thereof, mixtures of stereoisomeric forms thereof, pharmaceutically acceptable prodrugs thereof, or pharmaceutically acceptable salt forms thereof, wherein said compound is 7-(2-(R)-Butylamino)-

2,5-dimethyl-3-(2-methyl-4-methoxyphenyl)-[1,5-a]pyrazolopyrimidine.

3. A compound of claim 1, pharmaceutically acceptable prodrugs thereof, or pharmaceutically acceptable salt forms thereof, wherein said compound is substantially free of its (+) stereoisomer.

4. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 2.

5. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 3.

6. A method of antagonizing a CRF receptor in a mammal, comprising administering to the mammal, a therapeutically effective amount of a compound as claimed in claim 1.

7. A method of treating a disorder manifesting hypersecretion of CRF in a warm-blooded animal, comprising administering to the animal a therapeutically effective amount of a compound as claimed in claim 1.

8. A method for the treatment of a disorder, the treatment of which can be effected or facilitated by antagonizing CRF, comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.

9. A method of antagonizing a CRF receptor in a mammal, comprising administering to the mammal, a therapeutically effective amount of a compound as claimed in claim 3.

10. A method of treating anxiety or depression in mammals, comprising administering to the mammal a therapeutically effective amount of a compound of claim 1.

11. A method of treating anxiety or depression in mammals, comprising administering to the mammal a therapeutically effective amount of a compound of claim 3.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/06834

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/519 ; C07D 487/04
US CL :514/258 ; 544/281
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/258 ; 544/281

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6,136,809 A (GILLIGAN et al.) 24 October 2000 (24.10.00), see claims 1-4.	1-11

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

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